I. Listing of the Claims

Provided below is a listing of the claims in the present application.

1. (previously presented) A method of expressing a heterologous nucleic acid sequence in a vascular cell *in vivo* comprising administering to a blood vessel of a mammal a recombinant replicating herpes simplex viral vector lacking at least one expressible $\gamma_1$34.5 gene and operably comprising a heterologous nucleic acid.

2-4. (canceled)

5. (original) The method of claim 1, wherein the recombinant HSV vector lacks two expressible $\gamma_1$34.5 genes.

6. (original) The method of claim 1, wherein the vascular cell is an endothelial cell.

7. (original) The method of claim 1, wherein the vascular cell is a smooth muscle cell.

8. (original) The method of claim 1, wherein the vascular cell is an adventitial cell.

9. (original) The method of claim 1, wherein the heterologous nucleic acid sequence encodes a polypeptide.

10. (original) The method of claim 9, wherein the polypeptide is selected from the group consisting of an antiproliferative polypeptide, a vasodilatory polypeptide, and an angiogenic polypeptide.

11. (original) The method of claim 1, wherein the heterologous nucleic acid sequence encodes an antisense oligonucleotide or antisense polynucleotide.

12. (original) The method of claim 11, wherein the antisense oligonucleotide or antisense polynucleotide is complementary to an RNA encoding an antiproliferative polypeptide, vasodilatory polypeptide, or angiogenic polypeptide.

13. (original) The method of claim 1, wherein the herpes simplex virus is HSV-1.

14. (original) The method of claim 1, wherein the herpes simplex virus is HSV-2.

15-33. (canceled)

34. (previously presented) The method of claim 1, wherein the recombinant replicating herpes simplex virus is administered by a catheter.

35. (previously presented) The method of claim 34, wherein the catheter comprises a balloon.

36. (previously presented) The method of claim 1, wherein the blood vessel is an artery.

37. (previously presented) The method of claim 1, wherein the blood vessel is a vein.

38. (previously presented) The method of claim 1, wherein the blood vessel is the heart.

39. (previously presented) The method of claim 1, wherein the vascular cell is a neointimal cell.

40. (previously presented) The method of claim 1, wherein less than 10^9 pfu per ml of the vector is administered.

41. (previously presented) The method of claim 40, wherein less than 10^8 pfu per ml of the vector is administered.

42. (previously presented) The method of claim 1, wherein the heterologous nucleic acid sequence is expressed at least 7 days after the administration of the vector.

43. (previously presented) The method of claim 42, wherein the heterologous nucleic acid sequence is expressed at least 28 days after the administration of the vector.

44. (previously presented) The method of claim 43, wherein the heterologous nucleic acid sequence is expressed at least 70 days after the administration of the vector.

45. (previously presented) The method of claim 1, further comprising the step of administering to the mammal an amount of an antiviral agent effective to attenuate infection by the recombinant replicating herpes simplex viral vector.

46. (previously presented) The method of claim 1, further comprising the step of administering to the mammal an amount of an antiviral agent effective to eliminate infection by the recombinant replicating herpes simplex viral vector.

47. (previously presented) The method of claim 45, wherein the antiviral agent is a nucleoside analog.

48. (previously presented) The method of claim 46, wherein the antiviral agent is a nucleoside analog.

49. (previously presented) The method of claim 47, wherein the nucleoside analog is acyclovir or a pharmaceutically acceptable salt thereof.

50. (previously presented) The method of claim 48, wherein the nucleoside analog is acyclovir or a pharmaceutically acceptable salt thereof.

II. Outstanding Rejections

Claims 1, 5-14, and 34-50 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 5-14, and 34-50 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly not being enabled throughout the full scope of the claims.

Claims 1, 5-14, and 34-50 stand rejected under 35 U.S.C. § 102(b) and 35 U.S.C. § 103(a) as allegedly anticipated by or, in the alternative, obvious over Coffin *et al.*, Gene Ther. 3:560-566 (1996) (hereinafter, "Coffin (Gene Therapy)").

Claims 1, 5-14, and 34-50 stand rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Coffin *et al.* (WO98/04726) and Pyles *et al.*, WO 98/42195 (hereinafter, "Pyles").

III. Patentability Arguments

1. The Rejection under 35 U.S.C. § 112, second paragraph, should be withdrawn.

The rejection of claims 1, 5-14, and 34-50 under 35 U.S.C. § 112, second paragraph, was maintained for reasons of record provided in the official action mailed February 27, 2003, and because the claims fail to identify the heterologous genes (antisense and polypeptide-encoding), fail to state the results of practicing the claimed method with various heterologous genes in terms of detecting, measuring or treating, and fails to reveal the location of a heterologous gene within the vector such that the gene could be expressed in a vascular cell. Further, the official action notes that (1) a heterologous gene and (2) a HSV vector lacking an expressible $\gamma_1$34.5 gene are recited in the claims and are, therefore, essential limitations of those claims. In response, Applicant traverses the rejection.

The issue of indefiniteness, as with all patentability issues, is focused on the claimed subject matter. The pending claims are drawn to methods of using a HSV vector lacking at least one expressible $\gamma_1$34.5 gene (hereinafter, a $\gamma_1$34.5$^-$ HSV vector) to express a heterologous gene in a vascular cell. These claims are tailored to the inventors' contribution to the art that such HSV vectors could be used to express heterologous genes in vascular cells as opposed to, e.g., neuronal cells.

A $\gamma_1$34.5$^-$ HSV vector was known in the art as early as 1990 (*see* Chou *et al.*, Science 250:1262-1266 (1990), C8 of record). Moreover, the entire primary structure

of wild-type HSV has been known for years and these viruses have been exhaustively characterized. Given this state of the art, one of skill would know where to place a heterologous gene in such a vector. Further, the skilled worker would be able to turn to a number of well-known and straightforward assays for expression in vascular cells *in vitro* and *in vivo* to test any particular construct.

In addition to the knowledge in the art, the application disclosed a working example involving use of a HSV vector lacking at least one expressible $\gamma_1$34.5 gene and containing a heterologous gene (*lac*Z) to express that heterologous gene in a vascular cell. As taught in the specification, that heterologous *lac*Z gene was placed in operable linkage to the $\gamma_1$34.5 promoter. One of skill would recognize that placing a heterologous gene within an already mutated gene ($\gamma_1$34.5), or substituting the heterologous gene for the entire $\gamma_1$34.5 gene, would not affect the operability of the claimed method of expression. The vector lacked at least one expressible $\gamma_1$34.5 gene before placement of the heterologous gene and that status did not change after placement of the heterologous gene. Therefore, in view of the state of the art and the disclosure provided by the instant application, including working examples, one of skill would clearly and unambiguously understand that any of various locations in a HSV vector lacking at least one expressible $\gamma_1$34.5 gene would be suitable locations for placing a heterologous gene. This conclusion is consistent with the nature of Applicant's inventive contribution, which is that HSV vector lacking at least one expressible $\gamma_1$34.5 gene and containing heterologous genes can be used to express those genes in vascular cells. The pending claims are not drawn to a product, such as a vector or a particular recombinant molecule.

Applicant also maintains its position that the identity of a heterologous gene to be expressed in a vascular cell using a HSV vector lacking at least one expressible $\gamma_1$34.5 gene should not be a limitation in any of the claims. The claims are drawn to methods of using any of those vectors to express a heterologous gene in a vascular cell, not to treat a condition or disease in such a cell. One of skill in the art would recognize that use of a vector to express a heterologous gene in a particular type of cell, without more, would mean that the vector could be used to simply express any heterologous gene in that cell. Accordingly, while the presence of a heterologous gene in the HSV vector lacking at least one expressible $\gamma_1$34.5 gene may be a

limitation of the claim, the particular identity of the heterologous gene is not. The claimed methods are useful in expressing any heterologous gene.

The official action further maintained that the claims failed to state the results of practicing the claimed method with various heterologous genes in terms of reciting something that is detected, measured or treated and, thus, the claims omitted an essential limitation and are incomplete. The pending claims, however, are drawn to methods of expressing heterologous genes in vascular cells. The method expressly recites that the vector containing a heterologous gene is administered to a blood vessel of a mammal. As known in the art and as taught in the instant application, nothing more is required to achieve expression of a heterologous gene in a vascular cell. The claimed expression methods do not rely on quantitation for patentability and, in fact, do not include a limitation requiring quantitation. In addition, the claims are not drawn to treatment methods, but to expression methods; insistence on a limitation related to the results of treatment is inappropriate. Applicant has shown that, upon administration, a heterologous gene (e.g., *lacZ*) will be expressed in a vascular cell, exemplifying the subject matter of the claims. Nothing more is required and no further limitation should be required.

For all of the foregoing reasons, Applicant respectfully submits that the rejection of claims 1, 5-14, and 34-50 under 35 U.S.C. § 112, second paragraph, has been overcome and should be withdrawn.

2. The Rejection under 35 U.S.C. §112, first paragraph, should be withdrawn.

Claims 1, 5-14 and 34-50 stand rejected under 35 U.S.C. § 112, first paragraph, as assertedly not being enabled throughout the full scope of the claims. In support, the official action noted that the application did not teach the ramifications of expressing some heterologous genes, e.g., genes encoding anti-proliferative proteins, that the application did not address the risk of vector interactions in a cell harboring a latent virus, that the claims were drawn to subject matter in the unpredictable field of gene therapy, that Applicant admitted the vector was commercially available, and that the scope of enablement was less than the claim scope. In response, Applicant continues to maintain its respectful disagreement with the position of the office and continues to assert that, using the specification as a guide, one of ordinary skill in the

art can make and use the methods of the present claims without undue experimentation.

The claims are directed to a method of expressing a heterologous nucleic acid sequence in a vascular cell *in vivo*, comprising administering to a blood vessel of a mammal a recombinant replicating herpes simplex viral vector lacking at least one expressible $\gamma_1$34.5 gene and operably comprising a heterologous nucleic acid. The claims are not drawn to achieving a particular effect resulting from that expression, such as prolonged expression, or treatment of a disease or condition. Even if the heterologous gene encoded a gene product deleterious to a vascular cell, the harm to that cell would prove that the expression method was operable. Downstream uses, or even intentions, are not part of the claimed subject matter. Applicant has taught how to use HSV vectors lacking at least one $\gamma_1$34.5 gene operably linked to a heterologous gene to express that heterologous gene in a vascular cell. Regardless of the particular embodiment, be it expression of a therapeutically useful eukaryotic polypeptide, a therapeutically useful prokaryotic polypeptide, an antisense molecule, or a lethal gene product, the application taught how to make and use the claimed subject matter, which is simply expression of the genes encoding those gene products.

The official action also noted a concern that administering the vector to a vascular cell harboring a latent virus might lead to interactions that result in an active herpes infection. In response, Applicant notes that the HSV vectors lacking at least one expressible $\gamma_1$34.5 gene are relatively safe in being amenable to eradication with such toxic nucleotide analogs as acyclovir or gancyclovir (see Specification, Example 9). Thus, any interaction that resulted in an undesired active herpes infection could be controlled using one of these FDA-approved anti-viral drugs. Beyond this observation, Applicant is confident that, upon successful resolution of any patentability issues, FDA assessment of any health risk will result in approval of the claimed methods for expression of heterologous genes in vascular cells. (See M.P.E.P. 2107.03(V) and cases cited therein for the proposition that an invention may need to be disclosed as working as claimed, but it is improper to require a degree of effectiveness in treating humans.)

The official action also relied on the unpredictability characterizing the field of gene therapy. Applicant submits that the claimed subject matter is drawn simply to methods of expressing heterologous genes, not to any specific therapeutic, or treatment, methods. For that reason, Applicant submits that the field of the invention

is more precisely identified as recombinant gene expression rather than gene therapy. The field of recombinant gene expression, moreover, is predictable. Our understanding of heterologous gene expression, including heterologous prokaryotic, heterologous viral, and heterologous eukaryotic gene expression in particular cells has advanced to the point where expression cassettes have been developed to accommodate the expression characteristics of a given host cell, such as a vascular cell. The instant application has demonstrated that the heterologous prokaryotic *lacZ* gene was expressed according to the invention. Applicant submits that expression (not the ultimate use of an expression product) of a heterologous gene in a vascular cell is predictable and is not characterized by the unpredictability routinely attributed to a narrowly defined field of gene therapy.

Applicant also clarifies that, in its previous response, it did not admit that the HSV vector lacking at least one expressible $\gamma_1$34.5 gene was available for purchase. Applicant elaborated a hypothetical situation in which the vector was commercially available to establish that the clamed expression methods did not need to recite the step of placing the heterologous gene in the vector to satisfy the statutory requirements for patentability.

For all of the foregoing reasons, Applicant submits that the remarks provided herein have established that the pending claims are enabled throughout their full scopes. Accordingly, the rejection of claims 1, 5-14 and 34-50 has been overcome and should be withdrawn.

3. The rejection under 35 U.S.C. §102(b) as anticipated by, or in the alternative under §103(a) as obvious over, Coffin (Gene Therapy) should be withdrawn

Coffin (Gene Therapy) does not anticipate the pending claims. Claim 1 is directed to a method of expressing a heterologous nucleic acid sequence in a vascular cell *in vivo* comprising administering to a blood vessel of a mammal a recombinant replicating herpes simplex viral vector lacking at least one expressible $\gamma_1$34.5 gene and operably comprising a heterologous nucleic acid. Coffin (Gene Therapy) does not disclose administering to a blood vessel of a mammal a recombinant replicating herpes simplex viral vector lacking at least one expressible $\gamma_1$34.5 gene, and therefore Coffin (Gene Therapy) does not disclose each element of claim 1. Accordingly, Coffin (Gene Therapy) does not anticipate claim 1. All remaining claims are

dependent on claim 1 and, therefore, also include the limitations of claim 1. Thus, Coffin (Gene Therapy) does not disclose each of the elements of any of the pending claims and the withdrawal of the rejection of claims 1, 5-14, and 34-50 under 35 U.S.C. § 102(b) over Coffin (Gene Therapy) is respectfully requested.

Furthermore, Coffin (Gene Therapy) does not render any of the pending claims obvious under 35 U.S.C. § 103(a). As described on page 561 of Coffin (Gene Therapy) under "X-gal staining," it is effectively disclosed that viruses lacking $\gamma_1$34.5 and comprising a heterologous β-gal gene "gave only a relatively low number of blue staining cells" when primary rat cardiomyocytes were infected with such virus, and only a few blue staining cells when primary aortic vascular smooth muscle cells were infected. Moreover, the "Discussion" section (page 565) states that "deletion of ICP34.5, while preventing replication in [cardiomyocyte] cells, does not allow efficient gene delivery." Thus, Coffin (Gene Therapy) teaches that HSV viruses lacking $\gamma_1$34.5 are not efficient in expressing a heterologous nucleic acid in cardiomyocytes and vascular cells contacted *in vitro*.

Leaving aside the issue of the relevance of "efficiency" in gene delivery to the claimed subject matter, Coffin (Gene Therapy) teaches the relatively poor performance of the HSV lacking $\gamma_1$34.5 in providing gene expression in cardiomyocytes and vascular cells contacted *in vitro* relative to other mutant HSV (ICP27$^-$). Therefore, one of skill in the art would not be motivated to choose a HSV lacking a $\gamma_1$34.5 for *in vitro* administration of a heterologous gene to a vascular cell. More importantly, in shifting from an *in vitro* environment to the *in vivo* environment of the claims, one of skill would not be motivated to choose a vector shown to be a poor performer in an *in vitro* experiment. Thus, one of skill would not be motivated to administer an HSV lacking at least one expressible $\gamma_1$34.5, and operably comprising a heterologous gene, to a blood vessel *in vivo* for expressing a heterologous nucleic acid sequence. Indeed, Coffin (Gene Therapy) itself chose the ICP27-inactivated virus for *in vivo* gene delivery to the heart. Based on the foregoing reasoning, Applicant submits that there is no proper motivation for modifying the disclosure of Coffin (Gene Therapy) to arrive at the subject matter of any of the pending claims. Accordingly, the official action has failed to establish a *prima facie* case of obviousness for the subject matter of any of claims 1, 5-14 or 34-50 and the rejection of those claims under 35 U.S.C. § 103(a) over Coffin (Gene Therapy) has been overcome and should be withdrawn.

4. The rejection 35 U.S.C. §103(a) as being unpatentable over Pyles et al. (WO 98/42195) and Coffin et al. (WO 98/04726) should be withdrawn

In determining the obviousness of an invention, the prior art must be taken as a whole. M.P.E.P. § 2141.02. When the prior art is taken as a whole, one of skill in the art would not be motivated to administer a recombinant replicating herpes simplex viral vector lacking at least one expressible $\gamma_1$34.5 gene to a blood vessel of a mammal.

Pyles *et al.* discloses the administration of a particular double-mutant ($\gamma_1$34.5 and UNG) HSV to tumor cells. Coffin (WO98/04726) also discloses use of $\gamma_1$34.5 vectors. However, WO98/04726 does not describe administration of the $\gamma_1$34.5 vectors described therein to a blood vessel of a mammal. WO98/04726 merely lists heart in a laundry list of tissues that may be treated. When taking the prior art as a whole, Coffin (Gene Therapy) must be considered. In view of the teaching of Coffin (Gene Therapy) that $\gamma_1$34.5 deficient HSV vectors performed poorly in expressing a heterologous gene in vascular cells *in vitro*, the presence of heart in a laundry list of tissues would not be sufficient to motivate one of ordinary skill in the art to administer an HSV vector lacking at least one expressible $\gamma_1$34.5 gene to the blood vessel of a mammal. There is simply nothing in the art upon which the office has relied that points to the use of a $\gamma_1$34.5 vector as the vector to use to express a heterologous gene in a vascular cell. Thus, Pyles *et al.* and WO98/04726, alone or in combination, do not disclose or suggest administration of a recombinant replicating herpes simplex viral vector lacking at least one expressible $\gamma_1$34.5 gene to a blood vessel. Accordingly, Applicant submits that a *prima facie* case of obviousness over Pyles and Coffin (WO98/04726) has not been established for any of the pending claims.

Moreover, the Examples of the application disclosed the surprising and unexpected results requested by the Examiner. As discussed above, Coffin (Gene Therapy) describes the results of *in vitro* experiments wherein HSV vectors lacking $\gamma_1$34.5 and containing a heterologous gene did not efficiently provide expression of the heterologous gene in contacted primary cardiomyocytes and aortic vascular smooth muscle cells. Further, the article characterizes the results as indicating that "HSV may be inappropriate for highly efficient gene transfer to the arterial wall." Abstract. Regardless of the relevance of gene transfer efficiency to the claimed

subject matter, Coffin (Gene Therapy) expressly prefers HSV mutated in the gene encoding ICP27 to a HSV lacking $\gamma_1$34.5 for *in vitro* introduction and expression of a heterologous gene, a preference that was made even more apparent in the *in vivo* environment, where Coffin (Gene Therapy) did not even bother to use the HSV lacking $\gamma_1$34.5. Nothing in Pyles *et al.* or Coffin (WO 98/04726) contradicts this teaching of Coffin (Gene Therapy). Thus, in view of the cited art, one of skill in the art would not expect expression of a heterologous gene found in a HSV vector lacking at least one expressible $\gamma_1$34.5 gene in the variety of vascular cells disclosed in the application (e.g., neointimal, medial and adventitial cells) and would not expect the prolonged duration of expression also disclosed in the application.

Example 4 of the specification describes administration of a recombinant replicating herpes simplex viral vector lacking at least one expressible $\gamma_1$34.5 gene and operably comprising a heterologous nucleic acid (*lacZ*) to a blood vessel of a mammal (rabbit). Rather than the poor infectivity and expression reported within cells infected *in vitro* (Coffin), analysis of the blood vessel revealed surprisingly high infection efficiencies and *lacZ* expression in the adventitia, media, and neointima. Furthermore, the infection rates and stability of heterologous gene expression far exceeded the reported results with other vectors and at a dosage several orders of magnitude less than strategies using adenovirus (page 82, lines 15-25). Thus, in light of the teachings of the cited art, the method of the present claims provides surprising and unexpected results. Accordingly, even if a *prima facie* case of obviousness in view of Pyles and Coffin (WO98/04726) had been established, Applicant has demonstrated surprising and unexpected results sufficient to overcome that *prima facie* case. Accordingly, Applicant respectfully requests withdrawal of the rejection of claims 1, 4-15, and 34-50 under 35 U.S.C. §103(a) over Pyles and Coffin (WO98/04726).

CONCLUSION

For the forgoing reasons, it is submitted that each of claims 1, 5-14, and 34-50 are in condition for allowance. Should the examiner wish to discuss any further matter, he is invited to contact the undersigned at the number listed below.

Respectfully submitted,

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